REMARKS

The above amendments are submitted at the very helpful suggestions of the Examiner to more clearly set forth the inventive concept, and to conform their breadth to that of the scientific showing in the attached Rule 132 Declaration which establishes the unexpected advantages of 60-100mers in microarrays.

The additional language for the amended claims finds support throughout the specification. By example, "60 to about 120 nucleotide" language finds support at page 7, lines 25 and 26. "Long oligonucleotide" finds literal support at page 4, first line after Summary of the Invention. No new matter has been introduced by these amendments.

These amendments are provided to expedite the prosecution in the present filing, and are made without prejudice to a later filing. In view of the above amendments and the following remarks, the Examiner is respectfully requested to indicate the allowability of the claims as now amended.

The Examiner is thanked for the helpful interview held on October 17, 2002 with applicants' representative. During this interview, the rejections made in the October 15, 2002 Office Action and the newly cited art were discussed in view of providing a Rule 132 Declaration which would be more fully elucidating of the inventive concept, and limitations which could be provided in the claims to conform the breadth of the claims to the showing of the Declaration. The amendments above address the Examiner's concern that the prior Declaration was not commensurate in scope with the claimed invention.

The applicants have undertaken additional research in order to provide a further showing that there is a highly unexpected peak in sensitivity in the 60-120mer range, and have also provided documents which have demonstrated similar showings published by other laboratories and manufactures of microarrays. The additional research and identification of these references was accomplished to address the Examiner's recommendation during the 10/15/02 interview to provide oligos of at least 3 different lengths above and below the claimed rate so as to further illustrate the unexpected result for the claimed range of 60 to 120mers.

During the 10/15/02 interview, the Examiner suggested that if the specification does not teach labels other than radioactive, the claims should be so limited. Other labels are recited in

the specification. Please note at page 28, lines 21-28, chemically, photochemically, or enzymatically activated labeling compounds are noted, such as photobiotin, Dig-Che-Linc, as well as mimetics. At page 32, lines 15-23, fluorescent dyes (such as Cy 3 and Cy 5), isotopes such as P32 and P33, gold or silver particles with different scattering spectra, and enzymes for signal generations based on different substrate specificity of enzymes are recited. At page 33, lines 1 and 2, scintillation counting, autoradiographs, fluorescent measurement, colorimetric measures, light emission measurement and light scattering are also recited.

The Examiner has rejected previous Claims 9 and 36-38 under 35 U.S.C. §112, 2nd ¶ for indefiniteness, with helpful suggestions from the Examiner as to alternative claim language which would more clearly describe the present invention. In view of the above amendments to the claims to address her concerns, it is respectfully submitted that the claims as amended are now clearer and more definite. The Examiner is thanked for her thoroughness and efforts in this regards to provide the clearest possible claims.

Regarding Claim 9, the Examiner's note that "at least two sites" lacks proper antecedent basis in Claim 1 is well taken. Claim 1 has been amended to clarify that the probe oligonucleotide spots stably attached to the surface of a solid glass support at sites.

Regarding Claim 18, the Examiner's note that "unique" lacks proper antecedent basis in Claim 14 is well taken. At the Examiner's helpful suggestion, Claim 18 has been amended to replace "unique" with "long".

Regarding Claims 36-38, the Examiner has raised several concerns about structural elements which define or describe several phrases used therein. In order to expedite the present prosecution, the applicants have cancelled these claims without prejudice to their presentation in a continuing application.

Previous Claims 1-11, 14, 19 and 20 were rejected under 35 U.S.C. § 102 (e) as being anticipated by Ebersole. In making this rejection, the Examiner equates the Ebersole's 21 spot nucleotide configuration on a chromatographic bibulouse porous material which moves test samples laterally along the test strip by capillary migration with the nucleic acid microarray of the present invention. It is not conceded that the Ebersole invention is analogue art to the present microarray invention.

However, the Claims as now amended avoid Ebersole by restricting the scope of the claims to 60-120mers on a solid glass support. The Examiner's clear guidance in this regard is appreciated by the applicants, and the "about 50 to 100 nucleotides" of the prior claims has been amended to recite "60 to about 120 nucleotides". Even granting for arguments sake the Ebersole's configuration is equivalent to a microarray format, any potential inadvertent anticipation is avoided by the new limitations to the claims in view of Ebersole's limitation to 45-57 nucleotides.

The Examiner has also given further analysis to the remaining rejected claims. However, as all of these claims are dependant on Claim 1, which has been amended as above, these claims now avoid these concerns. The Examiner's comment regarding Claim 14, and the prior language "about 60 to 100 nucleotides" was very helpful to the applicants in modifying Claim 1 appropriately.

The Examiner has also rejected previous Claims 12, 13, 15-18, 21, 22 and 36-37 under 35 U.S.C. § 103(a), again over Ebersole as unpatentable over this teaching. The rejection of claims 36-37 have been obviated by their cancellation.

As discussed above in the remarks regarding the 35 U.S.C. § 102(e) rejection, the limitations provided in the amended claims obviate the Examiner's rejection. As all of the remaining objected to claims are dependant on Claim 1, which has been amended as above, these claims now avoid these concerns.

The Examiner has noted that, regarding Claim 18, "it is not inventive to discover the optimum by routine experimentation." However, please note that the attached Rule 132 Declaration clearly demonstrates that there was nothing routine about the experimental efforts of the inventors that culminated in the present invention. In fact, the inventors undertook the study for an entirely unrelated purpose, that is for the study of gene fragments to determine which segments had the strongest binding capacity to the sample (see Declaration bridging paragraph on page 2 up to Experimental Data on page 3)

First, there was a strong expectation from the scientific community that there was no advantage in sensitivity to be gained by increasing the length of the nucleic acid strands spotted on microarrays. Thus, there was no motivation to undertake such experimentation. In this regard, please note Dr. Munishkin's Declaration, citing the 1996 Schwille work, that:

"...the expectation of the research community was that there would be little or no increase in sensitivity of nucleic acid mixtures spotted on a microarray if their nucleic acid strand length was increased. " page 1, last full sentence

Dr. Munishkin goes on to explain that:

"Both studies in the published literature and practical experience with manufactured arrays indicated that the sensitivity of the cDNA arrays, which range upwards of 200mers, were comparable to the established 25mer arrays. These developments further entrenched the research community's assumption that an increased length of the NA spot did not increase sensitivity." Page 2, third full paragraph.

Therefore, the practitioner would not be motivated to undertake the effort of investigating possible optimization in this range.

Secondly, while oligonucleotide synthesis in the 60-120mer range was well known employing methods such as phosphoramidite protocols (by example see Specification, the sentence bridging pates 20 and 30), at the time of the filing of the subject application, the high cost of such materials would be highly discouraging for any potential application to microarray uses. Dr. Munishkin's Declaration addresses this aspect of the inventive process as follows:

"60-120mers of any reasonable quality cannot be produced using either the standard array synthetic methods still employed commercially by Affymetrix, or cDNA using PCR. While available commercially in 1999, materials of the 60-120mers were impractically priced for the many strands necessary for each spot provided in microarrays. The cost of 60-120mers was typically $220 for each DNA strand. 60-120mers were available from production house employing the existing, published literature on phosphoramidite chemistry." Page 2, 4th full paragraph

Dr. Munishkin concludes that:

"The literature and scientific community understanding in 1999, as well as cost considerations, would have strongly discouraged a researcher from investigating the use of 60-120mers on arrays. Not surprisingly, there was no reported experimentation into that possibility through this period." Page 2, 5th full paragraph

Therefore, given no motivation to increase sensitivity by producing nucleic acid spots in the 60-120mer range, and the substantial cost to do so, the inventors serendipitous use of oligos in this range to study binding specificity of gene fragments and their observation of completely surprising results cannot correctly be characterized as "routine experimentation".

Claims 23 and 38 have been rejected under 35 U.S.C. §103(a) as obvious over Ebersole in view of Van Ness, and Claim 35 has been rejected under the same paragraph over Stratagen. The rejection as to Claim 38 has been obviated by its cancellation. The rejection of Claim 23 and 35 is obviated by the showing of the Rule 132 Declaration attached, as explained above.

Prior Claims 1-3, 7, 8, 10-22 and 35-37 have been again rejected under 35 U.S.C. § 103(a) as obvious over Sheiness. The rejection of prior claims 36-37 have been obviated by their cancellation. The limitations provided to the remaining claims by amendment conform their breadth to the scope of the Rule 132 Declaration attached.

As with Ebersole, it is not conceded that the beaded dipstick of Sheiness is analogous to a microarray. However, as explained above, the attached Rule 132 Declaration clearly establishes that the experimentation undertaken by the inventors which serendipitously lead to the discovery of the inventive 60-120mer range with dramatically improved results was anything but routine experimentation.

Prior Claims 9, have been again rejected under 35 U.S.C. § 103(a) as obvious over Sheiness in view of Graves, and Claims 23 and 38 in view of Van Ness. With the amendments to the claims, including cancellation of Claim 38, and the discussion above, as well as in view of the Rule 132 Declaration attached, these rejections have been obviated.

The Examiner also commented on the prior Declaration. Her diligence in providing this insight is appreciated. The Examiner's comments were carefully reviewed. The current Declaration was developed specifically to address the Examiner's concerns.

The attached Rule 132 Declaration provides support to rebut a possible prima facia showing that the inventive 60-120mer range of nucleotide strand length is anticipated by Ebersole and/or Sheiness. The MPEP provides clear guidance as to how prima facie cases can be rebutted. Specifically, the MPEP teaches at § 2144.05 that:

> Applicants can rebut a *prima facie* case of obviousness based on overlapping ranges by showing the criticality of the claimed range. "The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

As such, the claimed narrow range of probe length can render the claims patentable over both Ebersole Sheiness if it can be shown that the claimed probe length embodies unexpected results.

In January of this year, the CAFC this year further clarified the *In re Geisler* case cited by the Examiner [*IN RE LANCE PETERSON* , CAFC 02-1129, decided January 8, 2003] The Court found that, in general, an applicant may overcome a prima facie case of obviousness by establishing that the "claimed range achieves unexpected results relative to the prior art range," the court stated, quoting *In re Geisler*, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997) (54 PTCJ 217, 7/17/97). That standard applies here when an applicant selects narrow ranges from broader ranges disclosed in the prior art, Judge Lourie wrote. Moreover, he added, the applicant's showing of unexpected results must be commensurate in scope with the claimed range.

CONCLUSIONS

Because the claimed nucleotide range of 60mers to about 120mers clearly provides unexpected results not suggested by the broad range of Ebersole or Sheiness, the Examiner's *prima facie* case of obviousness is successfully rebutted by the attached Rule 132 Declaration. This Declaration fully demonstrates the serendipitous nature of the inventors' discovery while working with gene fragments produced for the purpose of determining the specific sequences which had the best binding characteristics for a particular gene.

In view of the above amendments and remarks, and the attached Rule 132 Declaration, this application is considered to be in good and proper form for allowance. The Examiner is respectfully requested to so indicate at her earliest opportunity. If it may in anyway expedite the prosecution of this case, the Examiner is invited to contact the representative the applicants at the number below.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,

Date: 3/17/03

By: _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 1. (Amended) An array comprising at least one pattern of probe oligonucleotide spots stably attached to sites on the surface of a solid glass support, wherein each probe oligonucleotide spot of said pattern comprises an oligonucleotide probe composition made up of long oligonucleotide probes that range in length from 60 to about 120 ~~about 50 to 100~~ nucleotides.

2. (Amended) The array according to Claim 1, wherein two or more different target nucleic acids ~~are represented~~ hybridize to different probe oligonucleotide spots in said pattern.

8. (Amended) The array according to Claim 7, wherein ~~said~~ each of said long oligonucleotide probes is cross-linked to the surface of said support at least one site.

15. (Amended) The array according to Claim 14, wherein said array comprises ten or more different ~~target nucleic acids are represented~~ probe oligonucleotide spots in said pattern, each of which hybridizes to a different target nucleic acid.

18. (Amended) The array according to Claim 14, wherein each of said long ~~unique~~ oligonucleotides ranges from about 65 to 90 nucleotides in length..

36.-38 (Canceled)